

REMARKS

Claims 1-18 are pending and are the subject of the present Office Action. In the Office Action mailed July 20, 2001, the Examiner issued a Restriction Requirement under 35 USC 121, requiring restriction to one of the inventions of Groups I-VI. Applicants hereby elect to prosecute in the present application the inventions embodied by the claims of Group II identified by the Examiner. Claims 1-5 and 14-18 have been canceled without prejudice in the above amendment as being drawn to the non-elected inventions. Applicants do preserve the right to pursue claims directed to the non-elected inventions in further continuing applications.

Dependent claim 6 has been amended to incorporate the language of independent claim 1. The amendment to now independent claim 6 is not a narrowing amendment, but rather an amendment requested as a result of Applicants' election in the restriction requirement. The amendment should not be interpreted to adversely affect the full scope of the claim in any way. The amendments to claims 10-13 are likewise being made to change dependency, as a result of Applicants' election in the restriction requirement. Claims 19-43 have been added. Support for added claims can be found on at least pages 8, 9, 13, 14, 17, 18, 22, 28, 30, 34, and 42 of the specification.

The specification has also been amended to correct certain inadvertent typographical errors in various reference citations. It is submitted that no new matter has been introduced by these amendments.

The amendments to the specification and claims are illustrated on the attached pages entitled "Marked Up Version to Show Changes Made". For the Examiner's convenience, a clean copy of all the now pending claims 6-13 and 19-43 is provided above.

A Supplemental Information Disclosure Statement and Form 1449 are also enclosed herewith. In addition to the journal article reference listed on the Form 1449, Applicants wish to advise the Examiner of a pending US application, serial no. 09/048,641 filed March 26, 1998, of which Applicants' attorney is aware and which application may be material to the examination of the instant application. The

Examiner's consideration of these references is respectfully requested.

Respectfully submitted,

Date: August 16, 2001

By: *Diane L. Marschang*
Diane L. Marschang
Reg. No. 35,600

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-5416
Fax: (650) 952-9881



Marked Up Version to Show Changes Made

On pages 1-2, in the paragraph on lines 22-36 and 1-15, the text has been amended as follows:

---Various molecules, such as tumor necrosis factor- α ("TNF- α "), tumor necrosis factor- β ("TNF- β " or "lymphotoxin- α "), lymphotoxin- β ("LT- β "), CD30 ligand, CD27 ligand, CD40 ligand, OX-40 ligand, 4-1BB ligand, Apo-1 ligand (also referred to as Fas ligand or CD95 ligand), Apo-2 ligand (also referred to as TRAIL), Apo-3 ligand (also referred to as TWEAK), osteoprotegerin (OPG), APRIL, RANK ligand (also referred to as TRANCE), and TALL-1 (also referred to as BlyS, BAFF or THANK) have been identified as members of the tumor necrosis factor ("TNF") family of cytokines [See, e.g., Gruss and Dower, Blood, 85:3378-3404 (1995); Pitti et al., J. Biol. Chem., 271:12687-12690 (1996); Wiley et al., Immunity, 3:673-682 (1995); Browning et al., Cell, 72:847-856 (1993); Armitage et al. Nature, 357:80-82 (1992), WO 97/01633 published January 16, 1997; WO 97/25428 published July 17, 1997; Marsters et al., Curr. Biol., 8:525-528 (1998); Simonet et al., Cell, 89:309-319 (1997); Chicheportiche et al., [Biol. Chem.] J. Biol. Chem., 272:32401-32410 (1997); Hahne et al., J. Exp. Med., 188:1185-1190 (1998); WO98/28426 published July 2, 1998; WO98/46751 published October 22, 1998; WO/98/18921 published May 7, 1998; Moore et al., Science, 285:260-263 (1999); Shu et al., J. Leukocyte Biol., 65:680 (1999); Schneider et al., J. Exp. Med., 189:1747-1756 (1999); Mukhopadhyay et al., J. Biol. Chem., 274:15978-15981 (1999)]. Among these molecules, TNF- α , TNF- β , CD30 ligand, 4-1BB ligand, Apo-1 ligand, Apo-2 ligand (Apo2L/TRAIL) and Apo-3 ligand (TWEAK) have been reported to be involved in apoptotic cell death. Both TNF- α and TNF- β have been reported to induce apoptotic death in susceptible tumor cells [Schmid et al., Proc. Natl. Acad. Sci., 83:1881 (1986); Dealtry et al., Eur. J. Immunol., 17:689 (1987)]. ---

On pages 3-4, in the paragraphs on lines 22-36 and 1-24, the text has been amended as follows:

---Induction of various cellular responses mediated by such TNF family cytokines is believed to be initiated by their binding to specific cell receptors. Previously, two distinct TNF receptors of approximately 55-kDa (TNFR1) and 75-kDa (TNFR2) were identified [Hohman] Hohmann et al., J. Biol. Chem., 264:14927-14934 (1989); Brockhaus et al., Proc. Natl. Acad. Sci., 87:3127-3131 (1990); EP 417,563, published March 20, 1991; Loetscher et al., Cell, 61:351 (1990); Schall et al., Cell, 61:361 (1990); Smith et al., Science, 248:1019-1023 (1990); Lewis et al., Proc. Natl. Acad. Sci., 88:2830-2834 (1991); Goodwin et al., Mol. Cell. Biol., 11:3020-3026 (1991)]]. Those TNFRs were found to share the typical structure of cell surface receptors including extracellular, transmembrane and intracellular regions. The extracellular portions of both receptors were found naturally also as soluble TNF-binding proteins [Nophar, Y. et al., EMBO J., 9:3269 (1990); and Kohno, T. et al., Proc. Natl. Acad. Sci. U.S.A., 87:8331 (1990); Hale et al., J. Cell. Biochem. Supplement 15F, 1991, p. 113 (P424)].

The extracellular portion of type 1 and type 2 TNFRs (TNFR1 and TNFR2) contains a repetitive amino acid sequence pattern of four cysteine-rich domains (CRDs) designated 1 through 4, starting from the NH₂-terminus. [Schall et al., supra; Loetscher et al., supra; Smith et al., supra; Nophar et al., supra; Kohno et al., supra; Banner et al., Cell, 73:431-[435] 445 (1993)]. A similar repetitive pattern of CRDs exists in several other cell-surface proteins, including the p75 nerve growth factor receptor (NGFR) [Johnson et al., Cell, 47:545 (1986); Radeke et al., Nature, 325:593 (1987)], the B cell antigen CD40 [Stamenkovic et al., EMBO J., 8:1403 (1989)], the T cell antigen OX40 [Mallet] Mallett et al., EMBO J., 9:1063 (1990)] and the Fas antigen [Yonehara et al., supra and Itoh et al., Cell, 66:233-243 (1991)]. CRDs are also found in the soluble TNFR (sTNFR)-like T2 proteins of the Shope and myxoma poxviruses [Upton et al., Virology, 160:20-[29] 30

(1987); Smith et al., Biochem. Biophys. Res. Commun., 176:335 (1991); Upton et al., Virology, 184:370 (1991)]. Optimal alignment of these sequences indicates that the positions of the cysteine residues are well conserved. These receptors are sometimes collectively referred to as members of the TNF/NGF receptor superfamily. ---

On page 5, in the paragraph on lines 3-11, the text has been amended as follows:

---More recently, other members of the TNFR family have been identified. In von Bulow et al., Science, 278:138-141 (1997), investigators describe a plasma membrane receptor referred to as Transmembrane Activator and CAML-Interactor or "TACI". The TACI receptor is reported to contain a cysteine-rich motif characteristic of the TNFR family. In an *in vitro* assay, cross linking of TACI on the surface of transfected Jurkat cells with TACI-specific antibodies led to activation of NF-KB. [see also, WO 98/39361 published [September 18, 1998] September 11, 1998]. ---

On page 6, in the paragraph on lines 12-28, the text has been amended as follows:

---In Sheridan et al., Science, 277:818-821 (1997) and Pan et al., Science, 277:815-818 (1997), another molecule believed to be a receptor for Apo2L/TRAIL is described [see also, WO98/51793 published November 19, 1998; WO98/41629 published September 24, 1998]. That molecule is referred to as DR5 (it has also been alternatively referred to as Apo-2; TRAIL-R, TR6, Tango-63, hAPO8, TRICK2 or KILLER [Screaton et al., Curr. Biol., 7:693-696 (1997); Walczak et al., EMBO J., 16:5386-[5387] 5397 (1997); Wu et al., Nature Genetics, 17:141-143 (1997); WO98/35986 published August 20, 1998; EP870,827 published October 14, 1998; WO98/46643 published October 22, 1998; WO99/02653 published January 21, 1999; WO99/09165 published February 25, 1999; WO99/11791 published March

11, 1999]. Like DR4, DR5 is reported to contain a cytoplasmic death domain and be capable of signaling apoptosis. The crystal structure of the complex formed between Apo-2L/TRAIL and DR5 is described in Hymowitz et al., Molecular Cell, 4:563-571 (1999). --

On page 7, in the paragraph on lines 3-18, the text has been amended as follows:

---A further group of recently identified receptors are referred to as "decoy receptors," which are believed to function as inhibitors, rather than transducers of signaling. This group includes DCR1 (also referred to as TRID, LIT or TRAIL-R3) [Pan et al., Science, 276:111-113 (1997); Sheridan et al., Science, 277:818-821 (1997); [McFarlane] MacFarlane et al., J. Biol. Chem., 272:25417-25420 (1997); Schneider et al., FEBS Letters, 416:329-334 (1997); Degli-Esposti et al., J. Exp. Med., 186:1165-1170 (1997); and Mongkolsapaya et al., J. Immunol., 160:3-6 (1998)] and DCR2 (also called TRUNDD or TRAIL-R4) [Marsters et al., Curr. Biol., 7:1003-1006 (1997); Pan et al., FEBS Letters, 424:41-45 (1998); Degli-Esposti et al., Immunity, 7:813-820 (1997)], both cell surface molecules, as well as OPG [Simonet et al., supra; Emery et al., infra] and DCR3 [Pitti et al., Nature, 396:699-703 (1998)], both of which are secreted, soluble proteins. ---

On page 7-8, in the paragraph on lines 27-36 and 1-8, the text has been amended as follows:

---As reviewed recently by Tewari et al., TNFR1, TNFR2 and CD40 modulate the expression of proinflammatory and costimulatory cytokines, cytokine receptors, and cell adhesion molecules through activation of the transcription factor, NF- κ B [Tewari et al., Curr. Op. Genet. Develop., 6:39-44 (1996)]. NF- κ B is the prototype of a family of dimeric transcription factors whose

subunits contain conserved Rel regions [Verma et al., Genes Develop., 9:2723-2735 (1996); Baldwin, Ann. Rev. Immunol., 14:649-681 (1996)]. In its latent form, NF- κ B is complexed with members of the I κ B inhibitor family; upon inactivation of the I κ B in response to certain stimuli, released NF- κ B translocates to the nucleus where it binds to specific DNA sequences and activates gene transcription. As described above, the TNFR members identified to date either include or lack an intracellular death domain region. Some TNFR molecules lacking a death domain, such as TNFR2, CD40, HVEM, and GITR, are capable of modulating NF- κ B activity. [see, e.g., Lotz et al., J. Leukocyte Biol., 60:1-7 (1996)]. ---

In the claims:

Claims 1-5 and 14-18 have been canceled without prejudice.

The following claims have been amended:

6. (Amended) [The method of claim 1 wherein said agonistic antibody comprises an] A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to a synergistically effective amount of agonistic anti-DR5 receptor antibody and CPT-11.

10. (Amended) The method of claim [1] 6 wherein said agonistic anti-Apo-2 ligand receptor antibody is an antibody which cross-reacts with more than one Apo-2 ligand receptor.

11. (Amended) The method of claim [1] 6 further comprising exposing the cancer cells to one or more growth inhibitory agents.

12. (Amended) The method of claim [1] 6 further comprising exposing the cells to radiation.

13. (Amended) The method of claim [1] 6 wherein the cancer cells comprise colorectal cancer cells.

The following claims have been added:

---19. A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to a synergistically effective amount of agonistic anti-DR5 receptor antibody and CPT-11, wherein said agonistic anti-DR5 receptor antibody is a monoclonal antibody capable of inducing apoptosis in a mammalian cell expressing DR5 receptor.

20. The method of claim 19 wherein said mammalian cancer cells are exposed to said antibody and CPT-11 *in vitro*.

21. The method of claim 19 wherein said mammalian cancer cells are exposed to said antibody and CPT-11 *in vivo*.

22. The method of claim 19 wherein said agonistic anti-DR5 receptor antibody is a chimeric antibody.

23. The method of claim 22 wherein said chimeric antibody includes a variable or hypervariable domain of the anti-DR5 monoclonal antibody secreted by the hybridoma deposited as ATCC accession no. HB-12456 or by the hybridoma deposited as ATCC accession no. HB-12534.

24. The method of claim 19 wherein said agonistic anti-DR5 antibody binds to the same DR5 receptor epitope to which the anti-DR5 monoclonal secreted by the hybridoma deposited as ATCC accession no. HB-12456 or by the hybridoma deposited as ATCC accession no. HB-12534 binds.

25. The method of claim 19 wherein said agonistic anti-DR5 antibody is a human antibody.

26. The method of claim 19 wherein said agonistic anti-DR5 antibody specifically binds to DR5 receptor.

27. The method of claim 26 wherein said antibody has a DR5 receptor binding affinity of 10^8 M^{-1} to 10^{12} M^{-1} .

28. The method of claim 19 wherein said agonistic anti-DR5 receptor antibody inhibits binding of Apo-2 ligand to DR5 receptor.

29. The method of claim 19 wherein said agonistic anti-DR5 receptor antibody is a cross-reactive antibody which binds DR5 receptor and one or more other Apo-2 ligand receptors.

30. The method of claim 19 wherein said antibody is expressed in a recombinant host cell selected from the group consisting of a CHO cell, yeast cell and *E. coli*.

31. The method of claim 19 wherein said mammalian cancer cells are colon cancer cells or colorectal cancer cells.

32. A method of inducing apoptosis in mammalian colon or colorectal cancer cells comprising exposing mammalian colon or colorectal cancer cells to a synergistically effective amount of agonistic anti-DR5 receptor antibody and CPT-11, wherein said agonistic anti-DR5 receptor antibody is a monoclonal antibody capable of inducing apoptosis in a mammalian cell expressing DR5 receptor.

33. The method of claim 32 wherein said agonistic anti-DR5 receptor antibody is a chimeric antibody.

34. The method of claim 33 wherein said chimeric antibody includes a variable or hypervariable domain of the anti-DR5 monoclonal antibody secreted by the hybridoma deposited as ATCC accession no.

HB-12456 or by the hybridoma deposited as ATCC accession no. HB-12534.

35. The method of claim 32 wherein said agonistic anti-DR5 antibody binds to the same DR5 receptor epitope to which the anti-DR5 monoclonal secreted by the hybridoma deposited as ATCC accession no. HB-12456 or by the hybridoma deposited as ATCC accession no. HB-12534 binds.

36. The method of claim 32 wherein said agonistic anti-DR5 antibody is a human antibody.

37. The method of claim 32 wherein said agonistic anti-DR5 antibody specifically binds to DR5 receptor.

38. The method of claim 37 wherein said antibody has a DR5 receptor binding affinity of 10^8 M^{-1} to 10^{12} M^{-1} .

39. The method of claim 32 wherein said agonistic anti-DR5 receptor antibody inhibits binding of Apo-2 ligand to DR5 receptor.

40. The method of claim 32 wherein said agonistic anti-DR5 receptor antibody is a cross-reactive antibody which binds DR5 receptor and one or more other Apo-2 ligand receptors.

41. The method of claim 19 wherein said antibody is expressed in a recombinant host cell selected from the group consisting of a CHO cell, yeast cell and *E. coli*.

42. A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to a synergistically effective amount of agonistic anti-DR5 receptor antibody and CPT-11, wherein said agonistic anti-DR5 receptor antibody is a monoclonal antibody capable of inducing apoptosis in a mammalian

cell expressing DR5 receptor and binds to the same DR5 receptor epitope to which the anti-DR5 monoclonal secreted by the hybridoma deposited as ATCC accession no. HB-12456 or by the hybridoma deposited as ATCC accession no. HB-12534 binds.

43. A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to a synergistically effective amount of agonistic anti-DR5 receptor antibody and CPT-11, wherein said agonistic anti-DR5 receptor antibody is a chimeric antibody capable of inducing apoptosis in a mammalian cell expressing DR5 receptor and includes a variable or hypervariable domain of the anti-DR5 monoclonal antibody secreted by the hybridoma deposited as ATCC accession no. HB-12456 or by the hybridoma deposited as ATCC accession no. HB-12534.